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Renal Pathology at Autopsy in Patients Who Died after Hematopoietic Stem Cell Transplantation

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ABSTRACT

Acute and chronic renal dysfunction are common after hematopoietic stem cell transplantation (HSCT). Although the pathology of chronic HSCT nephropathy is well described, the histologic changes that accompany acute renal dysfunction after HSCT are less well known because renal biopsies are rarely undertaken in the peritransplantation period. Archival renal tissue from consecutive HSCT recipients who died and underwent autopsy at a single center during an 8-year period was studied. Abnormalities of renal pathology were described, and associations of histologic abnormalities with clinical events were systemically studied. Abnormalities of renal histology were common among the 26 patients in this study. The 3 most common histologic abnormalities were glomerular sclerosis (19/26; 73%), tubular epithelial atypia (19/26; 73%), and tubular calcification (18/26; 69%). Tubulitis (16/24; 67%) and interstitial fibrosis (16/26; 62%) were also frequently observed. Clinical veno-occlusive disease was not associated with histologic evidence of thrombotic microangiopathy in the kidney at autopsy. Also, clinical graft-versus-host disease was not associated with renal tubulitis. Unexpectedly, the proportion of patients with tubular atrophy (54%) or interstitial fibrosis (62%) was high, considering the young age of the patients at transplantation and their normal pretransplantation creatinine clearance. Well-recognized histologic abnormalities are common in the kidneys of patients who die after HSCT. Although we did not demonstrate associations of these histologic changes with clinical variables before death, larger studies with prospectively collected renal tissue are warranted.

KEY WORDS

Renal failure • Renal pathology • Hematopoietic stem cell transplantation

INTRODUCTION

Treatment-related toxicity limits the success of autologous and allogeneic hematopoietic stem cell transplantation (HSCT). Infection and bleeding during the period of marrow aplasia and treatment-related organ dysfunction remain major causes of nonrelapse mortality.

Renal insufficiency is a common organ dysfunction after HSCT. Acute renal insufficiency, defined as a doubling of the pretransplantation serum creatinine in the first 4 weeks after transplantation, occurs in 5% to 64% of HSCT recipients [1-4]. Approximately 25% to 50% of adult HSCT recipients who develop acute renal insufficiency require dialysis, and the requirement for dialysis confers a grave prognosis [1]. Many factors contribute to acute renal insufficiency after HSCT. Patients may have preexisting renal injury from their underlying disease, and prior therapy and high-dose chemotherapy and radiation administered in the preparative regimen may directly cause renal damage [5-7]. Rapid cytolysis of tumor and normal marrow can cause tumor lysis syndrome with renal injury due to hyperphosphatemia, as well as urate and xanthine nephropathy [8]. Infusion of cryopreserved marrow or blood progenitor cells may lead to renal insufficiency by several mechanisms. Dimethyl sulfoxide, a cryoprotectant, may cause in vivo

hemolysis and hemoglobinuria [9], and cellular debris accompanying cryopreserved cells causes direct glomerular damage and proteinuria [10]. Posttransplantation infections often lead to acute renal insufficiency because they may be accompanied by hypotension and renal hypoperfusion. Antimicrobials used for prophylaxis and treatment of infections are also commonly nephrotoxic. Finally, several HSCT-specific syndromes of organ dysfunction also affect the kidney. A hallmark of hepatic veno-occlusive disease is marked renal sodium avidity with renal dysfunction [3,11], and renal insufficiency is also a cardinal feature of post-HSCT hemolytic-uremic syndrome [12].

The pathology of renal injury in the immediate peritransplantation period is not well described. Renal biopsy is rarely undertaken early after transplantation, because patients are often severely thrombocytopenic. It is also unclear whether establishing the pathology of renal injury in the peritransplantation period would result in a specific treatment not otherwise considered.

In the longer term, 57% of patients in 1 series had a decrease of ≥20% in glomerular filtration rate at 2 years after HSCT [13]. Chronic renal dysfunction may result from incomplete recovery from acute peritransplantation renal insults, as well as from the effects of treatment of chronic graft-versus-host disease (GVHD) [14] and total body irradiation [13,14]. Although some suggest that cyclosporine nephrotoxicity is not a problem in this group [14,15], nephrotoxicity accompanying chronic GVHD is likely secondary to the use of calcineurin inhibitors rather than to GVHD itself [16].

In this report, we describe the renal pathology of 26 consecutive recipients of HSCT who died and underwent autopsy at a single transplant center. As prespecified hypotheses, we sought to examine whether clinical veno-occlusive disease was associated with renal thrombotic microangiopathy and whether acute and chronic GVHD were associated with renal tubulitis.

PATIENTS AND METHODS

Consecutive patients who died and underwent autopsy after high-dose therapy and HSCT at the Queen Elizabeth II Health Sciences Centre between June 1992 and January 2000 were included in this study. Renal pathology was assessed by a renal pathologist (R.G.) blinded to the clinical findings associated with each case. Kidneys were examined at autopsy by light microscopy with sections stained with hematoxylin and eosin, periodic acid-Schiff, Masson trichrome, and silver methenamine. Tissue retrieved from paraffin blocks was used for electron microscopy in cases of suspected glomerulopathy. The presence or absence of the following abnormalities was noted: thrombotic microangiopathy, glomerulopathy, glomerular sclerosis, tubular cell degeneration, tubular epithelial atypia (tubular epithelial cell pleomorphism and hyperchromasia), tubular calcification, tubular atrophy, tubulitis (lymphomonocytic infiltrate invading nonatrophic tubules), interstitial fibrosis, and arteriolar hyalinization. If the constellation of findings in a specimen was consistent with a specific renal diagnosis, this was also noted.

Clinical data were retrospectively extracted from the medical record by using a standardized form without knowledge of the pathologic findings. Acute and chronic GVHD and hepatic veno-occlusive disease were assessed clinically according to established criteria [17-19]. In this study, acute renal dysfunction was defined as a ≥50% increase in serum creatinine concentration (compared with the serum creatinine at transplantation) that was not present 2 weeks before death but that occurred in the 2 weeks immediately preceding death. Chronic renal dysfunction was defined as a ≥50% increase in serum creatinine above serum creatinine at transplantation present 2 weeks before death and sustained until the time of death.

Statistical analyses were performed with SPSS (SPSS Inc., Chicago, IL). The Student t test was used to describe differences between groups for continuous variables, and the Fisher exact test was used for discrete variables. Relationships among histologic observations were explored by using Spearman's ρ test without adjustment for multiple comparisons. Kaplan-Meier analysis was used to summarize the interval between transplantation and death. All statistical tests were 2 tailed, and $P \leq .05$ was considered significant.

RESULTS

Three hundred twenty-one patients (autologous, n = 180; related allogeneic, n = 130; unrelated allogeneic, n = 11) underwent HSCT at the Queen Elizabeth II Health Sciences Centre between June 1992 and January 2000, and 113 (35%) of these patients died within 3 years after HSCT. All 26 patients who died and underwent autopsy at the transplant center during this time are the subject of this report.

The patients' clinical characteristics at transplantation are shown in Table 1. All patients had a measured creatinine clearance of ≥60 mL/min before transplantation (mean, 120 mL/min; range, 67-172 mL/min). Most patients (20/26; 77%) underwent allogeneic transplantation, and all allogeneic recipients received cyclosporine and methotrexate as GVHD prophylaxis.

The causes of death and comorbidities of the 26 patients are shown in Table 2. Nonrelapse mortality (23/26; 88%) was the major cause of death, as expected, because the study was limited to patients who underwent autopsy at the transplant center. One pa-

Table 1. *Patient Characteristics at Transplantation*

Variable	Data
Age, y, mean (range)	37 (17-56)
Male sex, n (%)	19 (73%)
Indication for transplantation	
Acute leukemia	8
Lymphoma	6
Myeloma	5
Myelodysplasia	2
Chronic leukemia	2
Solid tumor	2
Aplastic anemia	1
Type of transplant, n (%)	
Autologous	6 (23)
Related allogeneic	16 (62)
Unrelated allogeneic	4 (15)
Pretransplantation creatinine clearance, mL/min, mean (range)	120 (67-172)
Etoposide conditioning, n (%)	5 (19)
Cyclophosphamide conditioning, n (%)	23 (88)
Total body irradiation, n (%)	5 (19)
Use of cyclosporine, n (%)	20 (77)

tient had clinical evidence of post-HSCT hemolytic-uremic syndrome before death.

The abnormalities of renal pathology of the 26 patients are shown in Table 3. The 3 most common histologic abnormalities were glomerular sclerosis (19/26; 73%), tubular epithelial atypia (19/26; 73%), and tubular calcification (18/26; 69%). The pattern of sclerosis was global in all cases of glomerular sclerosis, and the percentage of involved glomeruli was always <25%. Mild tubulitis (16/24; 67%) and interstitial fibrosis (16/26; 62%) were also frequently observed. Three clusters of abnormal renal pathologies were noted. Arteriolar hyalinization was associated with tubular cell degeneration ($\rho = 0.55$; $P = .003$) and tubular atrophy ($\rho = 0.39$; $P = .05$). Tubular cell degeneration and tubulitis were associated with glomerular sclerosis ($\rho = 0.41$, $P = .04$; and $\rho = 0.41$, $P = .05$, respectively), and interstitial fibrosis was associated with arteriolar hyalinization ($\rho = 0.42$; $P = .04$).

Table 3. *Renal Histologic Abnormalities*

Renal Histologic Abnormality	n (%)
Thrombotic microangiopathy	12 (46)
Glomerular sclerosis	19 (73)
Tubular cell degeneration	8 (31)
Tubular atrophy	14 (54)
Tubular epithelial atypia	19 (73)
Tubulitis*	16 (67)
Tubular calcification	18 (69)
Interstitial fibrosis	16 (62)
Arteriolar hyalinization	12 (46)

*Two cases were not evaluable for the presence of tubulitis because autolysis precluded interpretation of this abnormality (1 patient) and because of a marked infiltrate of polymorphonuclear cells (1 patient).

Two prespecified hypotheses of possible clinicopathologic associations were examined. The first hypothesis was that clinical veno-occlusive disease may be associated with histologic evidence of thrombotic microangiopathy in the kidney at autopsy. Although clinical veno-occlusive disease was present in 6 (23%) of 26 patients and histologic features of thrombotic microangiopathy (Figure 1) were common in the renal specimens at autopsy (12/26; 46%), no statistically significant association of these entities was noted ($P = .37$). The second hypothesis was that clinical GVHD may be associated with renal tubulitis at autopsy (Figure 2). GVHD manifests in other organs with a lym-

Table 2. *Causes of Death and Comorbidities*

Variable	Data
Interval between transplantation and death, mo, median (range)	3 (0.5-24)
Clinical acute or chronic GVHD, n (%)	10/20 (50)
Clinical veno-occlusive disease, n (%)	6/26 (23)
CMV-related disease, n (%)	3/26 (12)
Serum creatinine 2 wk before death, μmol/L, median (range)	97 (46-324)
Serum creatinine immediately before death, μmol/L, median (range)	187 (40-739)
Acute renal dysfunction, n (%)	15 (58)
Chronic renal dysfunction, n (%)	7 (27)
Causes of death, n (%)	
Nonrelapse	23 (88)
Noninfectious pulmonary disease	9
Infection	8
GVHD	2
Bleeding	2
Multiorgan failure	2
Relapse	3 (12)

CMV indicates cytomegalovirus.

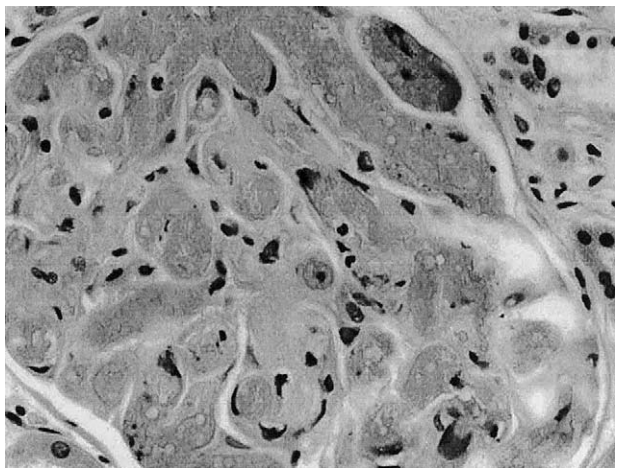

Figure 1. Renal thrombotic microangiopathy in a 38-year-old woman who died 7 months after an autologous transplantation for metastatic breast cancer. Before death, she had clinical evidence of posttransplantation hemolytic-uremic syndrome (stain, hematoxylin and eosin; magnification, 400×).

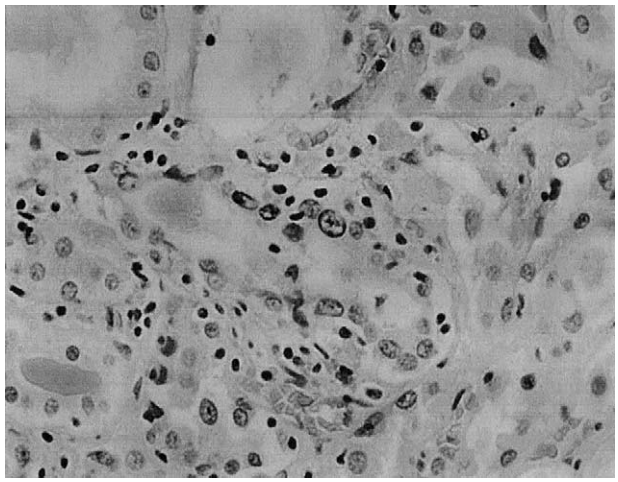

Figure 2. Renal tubulitis in a 51-year-old man who died 5 months after a matched sibling allogeneic transplantation for myeloma. Before death, he had extensive chronic graft-versus-host disease (stain, hematoxylin and eosin; magnification, 400×).

phocytic infiltrate of affected tissue. We reasoned that renal tubulitis may result from an infiltration of donor lymphocytes into the recipient's kidney, thus representing a renal manifestation of GVHD. However, we found no association of clinical acute or chronic GVHD with renal tubulitis ($P = .66$).

Tubular epithelial atypia was a common histologic abnormality (19/26; 73%) in the kidneys of the 26 patients. Etoposide, cyclophosphamide, and total body irradiation used in high doses as conditioning in HSCT are associated with well-described renal toxicities. However, we found no association between these agents and renal tubular epithelial atypia ($P = .59$, 1.0, and .59, respectively). There was also no histologic evidence of viral cytopathic effects in the renal specimens to account for the frequent observation of tubular epithelial atypia.

Two well-described clinicopathologic syndromes were observed among the 26 patients. One patient who underwent autologous transplantation for metastatic breast cancer died 7 months after HSCT of noninfectious pulmonary interstitial disease. At autopsy, she had glomerular basement membrane thickening consistent with membranous glomerulonephritis. Another patient who underwent a related allogeneic HSCT for myeloma had extensive chronic GVHD requiring long-term immunosuppression and died of disseminated aspergillosis. At autopsy, extensive renal infiltration with polymorphonuclear leukocytes and fungal elements was noted, compatible with the antemortem diagnosis of overwhelming fungal infection.

DISCUSSION

Acute renal dysfunction is common among patients undergoing HSCT. Multiple factors contribute to this renal dysfunction, including preexisting renal injury, direct effects of conditioning chemotherapy and radiation, complications of the infusion of cryopreserved cells, tumor lysis syndrome, and the effects of infection and its treatment. Hepatic veno-occlusive disease and post-HSCT hemolytic-uremic syndrome are also associated with renal insufficiency.

Despite the prevalence of clinical renal dysfunction in the peritransplantation period, little is known of the accompanying histologic changes in the kidney. Renal biopsy is rarely undertaken, because patients are often severely thrombocytopenic and clinicians judge that unexpected and treatable diagnoses are unlikely to be discovered.

We have described a spectrum of histologic abnormalities in the kidneys of 26 consecutive patients who died after HSCT and underwent autopsy at a single center. We found that renal histologic abnormalities were frequent in this population; thrombotic microangiopathy, tubular epithelial atypia, and arteriolar hyalinization were commonly observed. Given the complex clinical course these patients experienced in the days before their death, the expected renal lesion from hypoxia, ischemia, and toxic effects is acute tubular necrosis, which is characterized by a focal loss of tubular epithelial cells that leaves areas of denuded basement membranes [20]. We observed a high incidence of a number of abnormalities that were not in keeping with classic acute tubular necrosis.

First, tubulitis was seen in 67% of patients. Renal tubulitis without atrophy is an uncommon histologic diagnosis usually seen in renal allograft rejection and interstitial nephritis. In our patient group, no specific clinical factor was associated with this histologic abnormality at autopsy. In particular, renal tubulitis was not associated with GVHD. Second, thrombotic microangiopathy occurred in 46% of patients. The frequent histologic observation of renal thrombotic microangiopathy was also unexpected because only 1 patient had clinical evidence of hemolytic-uremic syndrome. This was not associated with veno-occlusive disease, a syndrome characterized histologically by hepatic microangiopathy and thrombosis. Although calcineurin inhibitors such as cyclosporine have been associated with post-HSCT hemolytic-uremic syndrome, we were unable to demonstrate an association between the use of cyclosporine and histologic changes of thrombotic microangiopathy in the kidney. However, the power of this analysis is limited because only 6 patients did not receive cyclosporine in our study.

Tubular epithelial atypia was another common abnormality of renal histology in this patient group. We hypothesized that tubular epithelial atypia may be related to specific cytotoxic agents or radiation used in the conditioning regimen. Cyclophosphamide is well known to affect the uroepithelium through its toxic

metabolite acrolein [21]. Etoposide is renally excreted and has been associated with renal dysfunction, and total body irradiation has well-described injurious effects on the kidney [22]. However, we did not observe an association between any of these agents and tubular epithelial atypia, nor was there evidence of viral cytopathic effects in the kidneys at autopsy to account for the tubular epithelial atypia. This frequent histologic abnormality remains unexplained.

The proportion of patients in this series with tubular atrophy or interstitial fibrosis was high (54% and 62%, respectively), considering their young age and normal creatinine clearance before transplantation. These histologic changes are typically chronic and unlikely to be related to immediate antemortem events. Although HSCT and the associated interventions and comorbidities may directly cause chronic renal injury, treatments administered before HSCT may also lead to subtle chronic renal injury that is not identified by measurement of creatinine clearance before transplantation.

One patient in this series had histologic features of membranous nephropathy. Her original diagnosis was breast cancer, and although the association between membranous nephropathy and solid-organ tumors is well known [23], the coexistence of this histologic pattern with breast cancer in particular has not been previously described. Membranous nephropathy was, however, observed by Imai et al. [14] in 2 of 9 cases after HSCT examined histologically; this raises the possibility of an association with HSCT rather than the underlying malignancy.

There are several limitations of our study. The histologic studies were limited by the use of archival autopsy material, which precluded immunologic and electron microscopic studies. The small number of autopsies performed at our center limited the power of the study to examine associations between clinical variables and histologic abnormalities, so our inability to document certain associations may have been solely due to the small patient sample size. Finally, although the study included consecutive patients who died after HSCT and underwent autopsy, it necessarily represents a selected group of patients. Patients who died after clinically apparent relapse would be less likely to have undergone autopsy, and patients who died at their local hospital or at home were not included in this study.

In summary, we have shown that well-recognized histologic abnormalities are common in the kidneys of patients who die after HSCT. In this small study, we did not demonstrate an association of renal thrombotic microangiopathy with either veno-occlusive disease or post-HSCT hemolytic-uremic syndrome. Renal tubulitis was not associated with acute or chronic GVHD. Larger studies with prospectively collected renal tissue for more detailed histologic study are warranted.

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